Basal ganglia-cortical structural connectivity in Huntington’s disease

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**Target Audience** Neurologists, Neuroscientists, Neuroimagers

**Purpose** Huntington’s disease (HD) is a genetic condition that affects both the white and grey matter of the brain. Striatal volume loss is the earliest and most characteristic structural abnormality seen using brain imaging in HD [1]. Voxel connectivity profiles (VCPs), such as the ones generated by Draganski et al [2], offer the potential to probe how basal ganglia connectivity patterns are affected by HD, but it remains unclear how best to exploit the rich data that are revealed by these methods. In this work we present a statistical method for comparing quantitatively between-group differences in VCPs using canonical variates analysis (CVA).

**Data** The cohort consists of 14 Huntington’s disease gene carriers with early symptoms (10 female; mean age=51.0±10.8 years), 17 premanifest Huntington’s disease subjects (10 female; mean age=41.2±8.7 years) and 18 sex-matched controls (10 female; mean age=44.6±10.1 years). The onset of manifest Huntington’s disease is defined as the point at which characteristic motor symptoms are seen: the subjects in this study were deemed manifest if they had scores of ≥5 in the motor section of the Unified Huntington’s Disease Rating Scale [3]. Data were acquired on a Siemens Tim Trio. Diffusion-weighting was applied in 64 non-collinear gradient directions at b=1000 s mm<sup>-2</sup> with an additional 8 b=100 s mm<sup>-2</sup> images for normalisation. Other settings: voxel size 2.3×2.3×2.3 mm<sup>3</sup>; in-plane resolution 96×96; 55 slices. Two T1-weighted structural images were also acquired using a 3D MPRAGE acquisition sequence; these were checked by eye and the better quality scan used for analyses. The structural imaging parameters were: TR=2200ms; TE=2.2ms; dimensions=256 pixels × 256 pixels × 208 sagittal slices per volume; slice thickness 1.0mm (no gap).

**Methods** Cortical and sub-cortical regions of interest (ROIs) were generated by segmenting the T1-weighted image using Freesurfer [4] and FSL’s [5] FIRST algorithm respectively. These targets were then warped into diffusion space by finding the mapping between the T1-weighted image and diffusion tensor fractional anisotropy (FA) map using FSL’s FNIRTregistration tool and applying the resulting warp to each of the ROIs. Probabilistic index of connectivity (PICO) tractography [6] was performed on data reconstructed using the multi-tensor model, as implemented in Camino [7]. For each basal ganglia ROI, 1000 streamlines were seeded per voxel and terminated when streamlines hit a cortical target, stepped outside of the brain mask or stepped into a region with an FA of less than 0.1. Connectivity matrices were generated by calculating the proportion of the 1000 streamlines from each seed voxel that terminated in each of the cortical targets, resulting in an N×27 matrix for each subject, where there were 27 cortical targets and N voxels in the seed ROI. The connectivity matrices were then thresholded at 1% and the total number of ROI voxels connected to each target was calculated to give a vector summarising the connectivity of the ROI. The vectors were then normalised by the total volume of the ROI to account for structure size. The statistical analysis proceeds as follows. First, the vectors for each subject were combined to form a matrix where each row corresponds to the subject and each column to a cortical target. The dimensionality of the data was then reduced using singular value decomposition (SVD). Finally, CVA was used to statistically compare the VCPs between groups.

**Experiments** We investigate group differences in the connectivity of the left and right caudate, putamen, pallidum, thalamus and nucleus accumbens. Prior to the data dimensionality reduction, we concatenate the connectivity information of all the regions together, which allows us to investigate overall changes in connectivity throughout the basal ganglia and thalamus in a single multivariate analysis.

**Results** Figure 1 shows an example of group VCPs of the putamen for the control (A), pre-manifest HD (B) and manifest HD (C) groups.

**Discussion and Conclusions** In this work we introduce a method for quantitative multivariate analysis of VCPs. We apply the method to analyse an HD cohort and show that the method is sensitive enough to detect significant differences between controls and early manifest HD. Inferences must be cautious with regard to individual connections because the test is inherently multivariate in nature, but the graphs suggest that altered structural connectivity in Huntington’s disease affects a high proportion of basal ganglia-cortical connections. The pattern of connectivity in the putamen, pallidum and thalamus appears most different from that of controls. Basal ganglia connectivity of premanifest HD patients was more similar to controls, which suggests there may be progressive changes throughout disease progression.


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